REMARKS

I. Status of Claims

Upon entry of this amendment, claims 1, 10, 26-28, and 30-32 are pending. Claims 1 and 26-28 have been amended. Claims 2-9, 11-23, 25, 29 and 33 are canceled. Claim 24 is withdrawn but includes a proposed amendment to keep the claim in conformity with claim 1 for rejoinder upon allowance of claim 1.

Amended claim 1 removes the 70% sequence identity limitation and as discussed below in Section III, is fully supported by the specification. Thus no new matter is added by this amendment. The amendments of the claims 26 to 28 merely correct claim dependencies and therefore also fail to add new matter.

II. Withdrawal of Rejections

Applicants thank the Examiner for withdrawing the rejections for new matter, enablement, and indefiniteness in the previous Office Action.

III. Rejection under 35 U.S.C. § 112, first paragraph, new matter

Claims 1 and those dependent therefrom amended in the previous response are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor had possession of the claimed invention and therefore rejected for containing new matter.

To the extent the rejection applies to the amended claims, Applicants respectfully traverse this rejection and its supporting remarks. "The test for written description in a parent application is whether the disclosure of the application relied upon '***reasonably*** conveys to one of skill in the art that the inventor had possession at that time of filing of the later claimed subject matter.'(emphasis added)" MPEP §2163.02 Further, written description requires only that the

specification convey to those of skill in the art that applicant at the time of filing the application was in possession of the invention as claimed, not that there be word for word support for the pending claims. This is made explicit by MPEP § 2163.02, which states "the subject matter of the claim need not be described literally (*i.e.*, using the same terms or *in haec verba*) in order for the disclosure to satisfy the written description requirement."

Amended claim 1 and those that depend therefrom are well supported in the specification and the originally filed claims. The specification indicates that "[t]he invention provides fragments of the proteins disclosed in international patent application WO99/36544, wherein the fragments comprise at least one antigenic determinant." See page 1, lines 24-25 and claim 1. SEQ ID NO:1331 is an amino acid sequence corresponding to a fragment of one of the proteins disclosed in WO99/36544, so the recitation of a "purified polypeptide comprising the amino acid sequence of SEQ ID NO:1331, wherein the polypeptide comprises at least one antigenic determinant" is clearly supported in the specification.

The immediately following paragraph indicates that the length "is preferably 100 amino acids or less ..." See page 1, lines 28-29. Thus, there is support for the recitation wherein the polypeptide "has a length of 100 amino acids or less."

Finally, there is support for the remaining recitation of claim 1 "wherein the polypeptide can detect the presence of antibodies raised against *Neisseria meningitidis* serogroup B ..." The specification indicates that the invention provides "the use of nucleic acid, ***protein***, or antibody ***according to the invention*** in the manufacture of: ... (ii) a diagnostic reagent for ***detecting the presence*** of a Neisserial bacteria or ***of antibodies against Neisserial bacteria***; ... Said Neisserial bacteria may be any species or strain (such as *N. gonorrhoeae*) but are preferably ***N. meningitidis***, especially strain A or ***strain B***." See page 3, lines 22-27. Furthermore, original claim 12, which depends from claim 1 directed to the fragments of the proteins in WO99/36544 (of which SEQ ID NO:1331 is), includes a similar use of the claimed fragments. Thus, one of skill in the art would easily recognize that the inventors had possession of the present claims because a polypeptide having the amino acid sequence of SEQ ID NO:1331 of 100 amino acids or less was a protein of the

present invention and that one use of the proteins of the present invention was to detect the presence of antibodies raised against *Neisseria meningitidis* serogroup B in a sample.

Finally, Applicants respectfully point out that the Examiner is incorrect in her assertion that the invention includes within its scope antibodies that recognize one of the 45 complete protein sequences in WO99/36544. The invention is directed towards polypeptides which "can detect the presence of the antibodies raised against *Neisseria meningitidis* serogroup B," not the antibodies themselves.

In view of the above remarks, Applicants respectfully assert that the amended claims have sufficient written description support in the specification and thus request withdrawal of the rejection.

IV. Rejection under 35 U.S.C. § 112, first paragraph, enablement

Claims 1, 10 and 25-32 have been rejected under 35 U.S.C. § 112, first paragraph, for lacking enablement. To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection and its supporting remarks. The specification as filed provides more than adequate support to enable one of skill in the art to make and use the claimed invention commensurate in scope with the claimed invention.

The specification must be taken as complying with the first paragraph of § 112 unless there is a reason to doubt the objective truth of the statements relied upon therein for enabling support (*In re Marzocchi*, 169 USPQ 367 (CCPA 1971)). The Examiner has not provided any reason to doubt that the specification is enabling for making or using of the presently claimed invention. In the response, the Examiner cites to multiple articles as support for her allegation that the presently claimed invention is unpredictable and therefore not enabled, but each and every one of these articles is inapplicable. The Examiner cites to two McGuinness *et al.* articles as showing that a single amino acid change within an epitope can have a drastic effect. However, these two articles, which document isolated examples of a single amino acid change affecting the immunological properties of the epitope, fail to speak to the overall predictability of alterations of

amino acids on antigenicity of polypeptides. The Examiner also cites to the teachings of Rudinger *et al.* regarding the structure-function relationship of amino acid sequence and biological activity. However, Rudinger is inapplicable as well because the structure-function requirements for antigenicity are vastly less rigorous than those for complex biological functions. Antigenicity is typically determined using software programs which analyze a combination of features, one of the most important of which is amino acid structure. In contrast, it is well known that biological functions of most proteins have multiple requirements beyond amino acid structure such as folding in a specific 3-D conformation and certain posttranslational modifications. The Examiner's final citation is to Houghten *et al.* However, this article and also each of the above-cited articles is irrelevant to the enablement rejection because the first McGuinness et al, the second McGuinness et al., Rudinger et al., and Houghten et al. articles were published respectively in 1991, 1993, 1976, and 1986. The priority date of the present application is July 14, 1999. In the intervening years between the publication of the cited references and the priority date, the state of the art has advanced so that what was unpredictable at the time of publication of the cited references is not necessarily still unpredictable. Thus, the Examiner has not cited to any evidence that would suggest that the presently claimed invention is not enabled.

Even if the Examiner had established a prima facie case of lack of enablement. Analysis of the so-called Wands factors demonstrate that undue experimentation is not required and therefore the invention as claimed is enabled. As indicated in *In re Wands*, undue experimentation is evaluated based upon multiple factors including the quantity of experimentation, the amount of direction or guidance provided, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above *Wands* factors while ignoring one or more of the others; instead, the Examiner's analysis must consider all the evidence related to each of these factors and any conclusion of nonenablement must be based on the evidence as a whole. § MPEP 21264.019(a). In this Office Action, the section regarding enablement, which spans five and a half pages, almost exclusively discusses the unpredictability of whether changes in amino acid

sequence would affect antigenicity of a polypeptide. The discussion of other *Wands* factors is limited to eight lines in the middle of page 7 regarding guidance in the specification. Thus the assertion that undue experimentation would be required is incorrect, as it is only supported by analysis of largely a single *Wands* factor. As demonstrated below, when the proper *Wands* analysis is conducted such that all of the factors are evaluated, they together support the assertion that undue experimentation is not required for one of skill in the art to make and use the invention commensurate in scope with the claims.

The first *Wands* factor is the quantity of experimentation necessary. The quantity of experimentation is not undue. The protein synthesis methods for the generating the polypeptides comprising SEQ ID NO: 1131 (fragment of ORF 114-1) and meeting the length limitations are routine and therefore not undue experimentation. Identifying the polypeptides with "at least one antigenic determinant" is routine given the wide availability of computer programs for antigen prediction, particularly in combination with the guidance provided by the other antigenic ORF 114-1 fragments disclosed in the specification. Finally, screening for polypeptides that can "detect the presence of antibodies raised against *Neisserial meningitidis* serogroup B in a sample" is routine, as it merely requires the use of well-established immunoassay methods to detect an interaction between the synthesized polypeptide to any antibody to *Neisseria meningitidis* serogroup B.

It is does not matter that it may take a fair amount of work to screen through multiple non-exemplified sequences to find those with an antigenic determinant and which are capable of detecting the presence of antibodies raised against *Neisserial meningitidis* serogroup B in a sample. The test for whether experimentation is undue is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

The second *Wands* factor is the amount of direction or guidance provided. As discussed with regard to the first *Wands* factor, the nature of the experimentation is all routine, so the techniques used need not be disclosed, and yet there is ample guidance throughout the specification.

Guidance regarding the preferred sequences of such polypeptides is provided, for example, at pages 64-71, which lists other predicted antigenic fragments of 114-1 (the full-length protein from which SEQ ID NO: 1331 is derived); and page 37, lines 9-29, which describes the software algorithms used to identify antigenic polypeptides. Immunoassays which can be used to identify polypeptides which detectably bind to *N. meningitidis* serogroup B antibodies are described on page 33, line 32, to page 34, line 4. Finally, the specification also provides general guidance to those of skill in the art regarding how to make the claimed polypeptides. For example, the specification describes how to make the polypeptides by recombinant expression or chemical synthesis. See, e.g., page 2, lines 18-22, and page 5, line 21 through page 21, line 3. Thus, there is a fair amount of guidance provided as how to identify and synthesize polypeptides which meet the limitations of the claims.

The third *Wands* factor is the presence or absence of working examples. As support for the rejection, the Examiner argues that there are no working examples. However, as made clear in MPEP §2164.01, working examples are not required to enable an invention. Thus the mere fact that the specification fails to disclose working examples of the presently claimed invention is insufficient grounds to conclude that the experimentation required to practice the invention is undue.

The fourth *Wands* factor is the nature of the invention. In this case, making and using the invention requires only routine molecular biology, protein synthesis, antigenic determinant prediction, and immunoassay techniques and thus the nature of the invention is one that requires only routine techniques that are well established.

The fifth *Wands* factor is the state of the prior art. The state of the art is high. As of the priority date of July 14, 1999, the techniques used to practice this invention were well worked out and included a high degree of automation due to the use of the software algorithms for predicting antigenic determinants and high-throughput immunoassays. Thus, one of skill in the art is capable of screening through large numbers of polypeptide sequences in order to identify additional polypeptides of this invention.

The sixth *Wands* factor is the relative skill of those in the art. The skill in the art is quite high as well. The methods used to practice this invention are typically performed by research scientists at the graduate level or higher. Such research scientists are well versed in the molecular biology, protein synthesis, antigenic prediction, and immunoassay techniques required by the claimed invention.

The seventh *Wands* factor is the predictability or unpredictability of the art. While the effect of variations of amino acid sequences of the claimed polypeptides cannot be predicted with one hundred percent accuracy, the vast body of knowledge regarding antigenicity based upon a number of different types of data including empirical evidence of what sequences are antigenic, structural and modeling studies of antigen presenting proteins that reveal the shape of the binding pocket and therefore the consensus sequences for antigens for each antigen presenting protein, and advances in immunology regarding how the immune system responds to novel antigens (factors which are all synthesized in antigenicity software prediction programs) provides some degree of predictability that will provide one of skill in the art with a starting point.

As discussed above, none of the articles cited to by the Examiner demonstrate the asserted unpredictability of the presently claimed invention as they are either unrelated to the claimed functionality or pre-date the priority date of the present invention that they are not relevant to the state of the art and therefore the predictability as of the priority date, which is when enablement is assessed.

Finally even if one were to concede that there was a high level of unpredictability (which is traversed), *Wands* makes clear that an invention can be enabled even when there is a complete lack of predictability. In this case, the Federal Circuit held that claims to monoclonal antibodies directed to a particular protein are enabled even where the application only discloses the sequence of the protein. Clearly, with just the protein sequence, one of skill in the art could not predict the sequence of even a single monoclonal antibody, much less all monoclonal antibodies that could bind to the protein. Nevertheless, despite the complete lack of unpredictability of the sequence of the monoclonal antibodies encompassed by the claim, the Federal Circuit still found such claims to be

enabled on the grounds that is was routine for one of skill to immunize an animal such as a rabbit with the protein, generate monoclonal hybridomas from the rabbit, and screen the hybridomas for monoclonal antibodies which are directed to the protein. Thus, *Wands* makes clear that other factors, such as the quantity of experimentation necessary, must be considered together with the degree of unpredictability when evaluating enablement, and are fully capable of compensating for even an extremely high degree of unpredictability.

The eighth *Wands* factor is the breadth of the claims. The claims are not unduly broad given that they are limited to a polypeptides which comprise a single polypeptide sequence and both the presence of an antigenic determinant and detection of antibody are features that can be easily screened for.

Thus given that most if not all of the *Wands* factors weigh in the favor of Applicants, the invention as claimed would not require undue experimentation by one of skill in the art to make and use the invention commensurate with the scope of the invention.

V. Conclusion

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. **03-1952** referencing docket no. 223002100200. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: August 20, 2007

Respectfully submitted,

By _____

Otis Littlefield
Registration No.: 48,751
MORRISON & FOERSTER LLP
425 Market Street
San Francisco, California 94105-2482
(415) 268-6846